



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

# Journal Pre-proof

Herpes zoster following COVID-19 vaccination in an immunocompetent and vaccinated for herpes zoster adult: A two-vaccine related event?

Natalia G. Vallianou, Dimitrios Tsilingiris, Irene Karampela, Junli Liu, Maria Dalamaga



PII: S2589-9368(22)00009-3

DOI: <https://doi.org/10.1016/j.metop.2022.100171>

Reference: METOP 100171

To appear in: *Metabolism Open*

Received Date: 29 January 2022

Revised Date: 8 February 2022

Accepted Date: 9 February 2022

Please cite this article as: Vallianou NG, Tsilingiris D, Karampela I, Liu J, Dalamaga M, Herpes zoster following COVID-19 vaccination in an immunocompetent and vaccinated for herpes zoster adult: A two-vaccine related event?, *Metabolism Open* (2022), doi: <https://doi.org/10.1016/j.metop.2022.100171>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2022 Published by Elsevier Inc.

All authors have had access to the data and results and have reviewed and approved the latest version of the manuscript.

CRediT statement: Natalia G. Vallianou: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. Dimitrios Tsilingiris: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. Irene Karampela: Investigation, Writing – review & editing; Junli Liu: Investigation, Writing – review & editing. Maria Dalamaga: Conceptualization, Investigation, Writing – original draft, Writing – review & editing.

# **Herpes zoster following COVID-19 vaccination in an immunocompetent and vaccinated for herpes zoster adult: a two-vaccine related event?**

**Natalia G. Vallianou<sup>1\*</sup>, Dimitrios Tsilingiris<sup>2\*</sup>, Irene Karampela<sup>3</sup>, Junli Liu<sup>4</sup>, Maria Dalamaga<sup>5</sup>**

<sup>1</sup>First Department of Internal Medicine, Evangelismos General Hospital, 45-47 Ipsilantou str, 10676 Athens, Greece

<sup>2</sup>First Department of Propaedeutic Internal Medicine, School of Medicine, National and Kapodistrian University of Athens, Laiko General Hospital, 17 St Thomas street, 11527 Athens, Greece

<sup>3</sup>Second Department of Critical Care, Attikon General University Hospital, Medical School, National and Kapodistrian University of Athens, 1 Rimini St, Haidari, 12462 Athens, Greece

<sup>4</sup>Shanghai Jiao Tong University School of Medicine, Shanghai Jiao Tong University Affiliated 6th People's Hospital, Shanghai Diabetes Institute, Shanghai, China

<sup>5</sup>Department of Biological Chemistry, School of Medicine, National and Kapodistrian University of Athens, 75 Mikras Asias, 11527 Athens, Greece

\*These authors contributed equally

**Conflict of interest statement:** No conflict of interest to disclose

**Financial support:** None

**Corresponding author:**

**Dimitrios Tsilingiris**, MD, PhD  
National and Kapodistrian University of Athens,  
Medical School,  
75 Mikras Asias, 11527 Athens, Greece  
e-mail: [tsilingirisd@gmail.com](mailto:tsilingirisd@gmail.com)

**Maria Dalamaga**, MD, MSc, MPH, PhD  
National and Kapodistrian University of Athens,  
Medical School,  
75 Mikras Asias, 11527 Athens, Greece  
e-mail: [madalamaga@med.uoa.gr](mailto:madalamaga@med.uoa.gr)

**Abstract**

Reactivation of varicella-zoster virus (VZV) has been reported after the administration of different vaccine platforms against SARS-CoV-2, also among individuals without known immunosuppressive states. Herein, we describe for the first time a case of herpes zoster after mRNA vaccination against SARS-CoV-2 in a 53-year-old immunocompetent adult without any known comorbidities, who was previously vaccinated with a live attenuated zoster vaccine. The fact that the patient had no history of varicella and had been tested seronegative for VZV prior to immunization with the live attenuated zoster vaccine further contribute to the challenge of this unusual case. This advocates for a high level of vigilance on the part of clinicians regarding this rare complication among receivers of COVID-19 vaccines.

**Keywords:** COVID-19; mRNA; Herpes Zoster; live attenuated

## 1. Introduction

As mass vaccination programs against COVID-19 are ongoing worldwide, physicians are witnessing a wide range of adverse events [1, 2]. Recently, reactivation of varicella-zoster virus (VZV) has been reported after administration of different vaccines against SARS-CoV-2, although causality is still under investigation. VZV reactivation is principally attributed to perturbations of the immune status and age of the patients, with altered immunocompromised state and senescence being the most significant risk factors. The development of herpes zoster (HZ) has been reported as a side effect following vaccination with mRNA vaccines in patients, with or without known immunosuppression [1, 3, 4]. Herein, we describe for the first time an interesting case of herpes zoster after mRNA vaccination against SARS-CoV-2 in a 53-year-old immunocompetent adult without any known comorbidities who was previously vaccinated with a live attenuated zoster vaccine (Zostavax).

## 2. Case Report

A 53-year-old male patient with a body mass index of 24.2 kg/m<sup>2</sup>, presented to the Outpatient Clinic of the hospital due to a painful erythematous rash on his right upper back which appeared eleven days after receiving the first dose of BNT162b2 mRNA COVID-19 (Pfizer-BioNTech) vaccine (Figure 1). His medical history was negative with respect to chronic illnesses, and he was currently not receiving any medication. On further anamnestic questioning, the patient reported never having been ill with chickenpox. Regarding his vaccination history apart from the recent COVID-19 vaccine, the patient had received a full live attenuated herpes zoster vaccination two years before on the basis of negative VZV antibody serologic testing. He reported no contacts with patients with chickenpox or shingles thereafter. Other than a herpetiform, vesicular and erythematous rash with a zosteriform pattern on the distribution of the 6<sup>th</sup> thoracic dermatome of his right hemithorax, further physical examination was unremarkable.

Based on his past medical history, his clinical presentation with the typical HZ rash morphology and distribution as well as burning pain, a provisional diagnosis of vaccine-strain related herpes zoster was made. The patient received valacyclovir 1000mg thrice daily for seven days with subsequent resolution of the rash. His clinical course was favorable, although he reported postherpetic neuralgia for over a month. After a 10-day delay in the vaccination schedule, he received the second dose BNT162b2 which was well tolerated, while no further HZ recurrences were observed after both the second and third (booster) doses.

### 3. Discussion

Zostavax, the live-attenuated VZV vaccine is highly effective in the prevention of HZ and postherpetic neuralgia. In a study among 38,546 adults aged over 60, vaccination reduced the 3.1-year incidence of HZ and post-herpetic neuralgia vs. placebo by 51.3% and 66.5%, respectively [5, 6]. Efficacy against VZV has also been shown to be high among individuals aged between 50-59 years (approximately 70% over a median 1.3 years vs. placebo [7]). Overall, the clinical course of a typical Herpes-Zoster appearance on our previously live-attenuated VZV-vaccinated patient who was anamnestic and serologically negative for a previous chickenpox infection raises the question of a possible reactivation of the latent VZV-vaccine viral strain. It has been established that a latent infection with the live-attenuated viral strain (vOka) can occur after vaccination, and subsequent Herpes Zoster thereafter may occur through reactivation of the wild-type virus or due to vOka, although the latter appears to be extremely rare [8, 9]. An alternative possibility would include the unlikely assumption that our patient acquired a wild-type VZV after vaccination with Zostavax, without having exhibited clinical signs of overt chickenpox. A past, currently not recalled chickenpox illness could be a third plausible explanation, although the negative anti VZV-IgG antibodies prior to vaccination present a solid counterargument against this scenario.

Furthermore, in our patient, the occurrence after eleven days of the COVID-19 vaccine support the possibility of a relationship with the recent COVID-19 vaccination. Although the timely association with the mRNA-platform vaccination does not prove causality between the two events, there is accumulating evidence highlighting the increased incidence of VZV reactivation following COVID-19 vaccination, not only from the mRNA-based vaccines, but also from the adenovirus-vector and inactivated vaccines, as well [1-3, 10]. A total of 2,527 cases of VZV infection following vaccination against SARS-CoV-2 have been reported in the United Kingdom until today [1]. Most cases have been linked to the immunosuppression of the host-recipient of the vaccine. However, there are also cases in immunocompetent individuals [1-3]. It is widely known that the immune system responds with a significant T-cell activation after COVID-19 vaccination [1, 2]. More specifically, increased CD8<sup>+</sup> T cell and T helper type 1 CD4<sup>+</sup> T cell counts have been demonstrated to occur after administration of mRNA-based vaccines for SARS-COV-2 [2]. A plausible explanation is that VZV-specific CD8<sup>+</sup> cells are not able to preserve the VZV latent state after the massive shift of naïve CD8<sup>+</sup> cells in the context of SARS-CoV-2 vaccination [2]. Another hypothesis suggests that alterations in Toll-like receptor expression among vaccinated people are associated with enhancement in type I interferon and pro-inflammatory cytokines leading to immunogenicity for the COVID-19 vaccine at the cost of reactivation of VZV [1, 3, 3].

A major limitation of our report concerns the lack of identification of the VZV strain implicated in this clinical case due to the lack of availability of a corresponding real-time polymerase chain reaction assay, so that the dominant working hypothesis of an vOka-strain related zoster cannot be definitely proven. In either case, the occurrence of herpes zoster in an immunocompetent and otherwise healthy patient, previously vaccinated against VZV is certainly an unexpected event, which warrants for a high level of vigilance on the part of clinicians regarding this rare complication among recipients of COVID-19 vaccines.



## Conflicts of Interest

None declared

## References

- [1] Katsikas Triantafyllidis K, Giannos P, Mian IT, Kyrtsionis G, Kechagias KS. Varicella Zoster Virus Reactivation Following COVID-19 Vaccination: A Systematic Review of Case Reports. *Vaccines*. 2021;9, doi:10.3390/vaccines9091013.
- [2] Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines - a new era in vaccinology. *Nature reviews Drug discovery*. 2018;17:261-79, doi:10.1038/nrd.2017.243.
- [3] Furer V, Eviatar T, Zisman D, Peleg H, Paran D, Levartovsky D, et al. Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study. *Annals of the rheumatic diseases*. 2021;80:1330-8, doi:10.1136/annrheumdis-2021-220647.
- [4] Psychogiou M, Samarkos M, Mikos N, Hatzakis A. Reactivation of Varicella Zoster Virus after Vaccination for SARS-CoV-2. *Vaccines*. 2021;9, doi:10.3390/vaccines9060572.
- [5] Oxman MN, Levin MJ, Johnson GR, Schmader KE, Straus SE, Gelb LD, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *The New England journal of medicine*. 2005;352:2271-84, doi:10.1056/NEJMoa051016.
- [6] Oxman MN, Levin MJ, Shingles Prevention Study G. Vaccination against Herpes Zoster and Postherpetic Neuralgia. *The Journal of infectious diseases*. 2008;197 Suppl 2:S228-36, doi:10.1086/522159.
- [7] Schmader KE, Levin MJ, Gnann JW, Jr., McNeil SA, Vesikari T, Betts RF, et al. Efficacy, safety, and tolerability of herpes zoster vaccine in persons aged 50-59 years. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2012;54:922-8, doi:10.1093/cid/cir970.
- [8] Tseng HF, Schmid DS, Harpaz R, LaRussa P, Jensen NJ, Rivailler P, et al. Herpes zoster caused by vaccine-strain varicella zoster virus in an immunocompetent recipient of zoster vaccine. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2014;58:1125-8, doi:10.1093/cid/ciu058.
- [9] Weinmann S, Chun C, Schmid DS, Roberts M, Vandermeer M, Riedlinger K, et al. Incidence and clinical characteristics of herpes zoster among children in the varicella vaccine era, 2005-2009. *The Journal of infectious diseases*. 2013;208:1859-68, doi:10.1093/infdis/jit405.
- [10] Arora P, Sardana K, Mathachan SR, Malhotra P. Herpes zoster after inactivated COVID-19 vaccine: A cutaneous adverse effect of the vaccine. *Journal of cosmetic dermatology*. 2021;20:3389-90, doi:10.1111/jocd.14268.

**Legend to Figure 1:** The improved vesicular rash of the patient in a resolution course after completion of valacyclovir treatment

